Remarks

Claims 23-34 are pending in the subject application. By this Amendment, Applicants have canceled claims 26, 29, and 32-34 and amended claims 23 and 24. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 23-25, 27, 28, 30, and 31 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

The Examiner indicates that the reference listed as "O" in the Information Disclosure Statement (IDS) filed 2/11/2002 is not in conformance with M.P.E.P § 609 and has not been considered because there is no publication date and no indication as to where the cited reference was first published. Applicants would like to bring to the Examiner's attention a Second Supplemental Information Disclosure Statement resubmitting the Jacobs *et al.* reference (listed as "O" on the IDS filed 2/11/02) and listing additional references for consideration in the prosecution of the subject application which is being submitted in conjunction with the filing of this Amendment. Applicants respectfully request that the references be considered and made of record by the Examiner in the subject application.

The drawings have been objected to under 37 C.F.R. § 1.84 or 1.152. Applicants have submitted with this Amendment formal Figure 1 in response to the Notice of Draftsperson's Patent Drawing Review. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 23 and 24 are objected to because of informalities. Applicants gratefully acknowledge the Examiner's careful review of the claims. In accordance with the Examiner's suggestion, Applicants have replaced the phrase "an amino acid sequence of SEQ ID NO: 399" with "the amino acid sequence of SEQ ID NO: 399" in claims 23 and 24. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 26, 29, and 32 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement. Claims 26, 29, and 32 have also been rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for the polypeptide of SEQ ID NO: 399, does not reasonably enable an allelic variant of the polypeptide of SEQ ID NO:

399. While Applicants respectfully disagree with the position of the Patent Office with respect to these rejections, the claims have been canceled in the interest of expediting prosecution in this matter. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 25, 28, and 31 have been rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Office Action indicates that the claims contain subject matter that is not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Particularly, the Office Action argues that the claimed invention requires the clone 160-40-1-0-H4-CS (deposited with the ATCC as PTA-1218). Submitted herewith is a statement by the undersigned indicating that the clone has been deposited under the terms of the Budapest Treaty and that the clone will be irrevocably, and without restriction or condition, released to the public upon the issuance of a patent in this matter.

Applicants note that the Office Action indicates that U.S. Patent Application Serial No. 09/731,872 discloses a polypeptide identical to that of SEQ ID NO: 399 of the instant application. Applicants wish to bring to the Examiner's attention that a divisional application (having U.S. Patent Application Serial No. 10/643,836) has been filed from the '872 application.

Claims 23-34 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by a well-established utility or by a specific and substantial utility. Claims 23-34 are also rejected under 35 U.S.C. §112, first paragraph, on the basis that one skilled in the art would not know how to use the claimed invention because it is not supported by a well-established utility or by a specific and substantial utility. The Office Action argues that the asserted function of the claimed polypeptide is based solely upon structural homology and the specification does not provide any empirical evidence that the polypeptide is a phosphatidic acid phosphatase. The Office Action also asserts that the percentage of homology between SEQ ID NO: 399 and human PAP type 2C, 2B, and 2A is 18.4%, 17.9%, and 17.8% respectively. The Examiner further asserts that the fragment of SEQ ID NO: 399 that comprises the Pfam domain of the PAP2 superfamily shows a percentage of homology of 21.4%, 20.8, and 20.6% with the corresponding fragment of human PAP2 type 2C, 2B, or 2A. The Examiner also cites six articles suggesting that structural homology alone is not sufficient to predict a polypeptide's function. Thus the Examiner alleges that the function assigned

to SEQ ID NO: 399 is not credible, and that further research is required to identify a "real word" context of use. Applicants respectfully traverse.

Applicants respectfully submit that the identification of the claimed polypeptide as a member of the PAP2 family is not based on sequence alignment alone. Rather, Applicants have identified a Pfam domain using Hidden Markov Modeling (HMM) analysis, not sequence alignment. The result of the HMM analysis is shown in attached Appendix 1. Applicants respectfully submit that the e-value obtained for the PAP2 Pfam domain present in SEQ ID NO: 399 is of $8.6e^{-14}$, which is a highly significant score. Accordingly, one of skill in the art would reasonably believe that SEQ ID NO: 399 belongs to the PAP2 superfamily. In addition Applicants submit that SEQ ID NO: 399 not only displays a PAP2 Pfam domain, but also displays the following conserved phosphatase signature motif: T-X_6-[R]P-X_{34}-PSG[H]-X_{48}-SR-X_5-H-X_3-D. As taught by Stacey *et al.*, this conserved motif can serve as a predictor of phosphate enzyme function (see page 471, column 1, line 42-43 of Stacey *et al.*).

In Stacey *et al.* it is stated that:

> The following existing experimental evidence supports the identification of this phosphatase signature motif:
>
> a) These conserved sequences are conceptually present in 13 known phosphatases; (...)
>
> b) Structure function analysis of the human glucose-6-phosphatase indicates two of the absolutely conserved residues *[the arginine and the histidine highlighted by a box in the above consensus sequence]* are essential for enzyme function; and
>
> c) A current database "hypothetical" gene product (Accession No. U51031) having this phosphate signature motif has been identified as a diacylglycerol pyrophosphate phosphatase. (see page 471, column 1, lines 47-60 of Stacey *et al.*)

Accordingly, in view of the presence of (1) a highly significant PAP2 Pfam domain; and (2) a phosphatase signature motif displaying the two absolutely conserved residues essential for enzyme

function, one of skill in the art would reasonably conclude that SEQ ID NO: 399 is a phosphatidic acid phosphatase.

Moreover, Applicants respectfully submit that the references cited by the Examiner fail to establish that the function assigned to SEQ ID NO: 399 based on a bioinformatics analysis is not credible. As indicated above, the function of SEQ ID NO: 399 was not assigned by pair wise searching but by identification of motifs. Attwood *et al.* teaches that:

> *Gene family databases allow more specific functional diagnoses* to be made than is possible by pair wise searching. They are based on the principle that related sequences can be aligned to find motifs that show little variation. *These motifs usually reflect some vital structural and functional role*, and they can be used to derive diagnostic family signatures (see page 2, fifth paragraph of the copy provided by the Examiner; emphasis added).

Applicants note that in the articles by Van de Look *et al.*, Seffernick *et al.* and Broun *et al.*, the function predicted for the proteins was based on sequence alignments – not on the presence of Pfam domains and/or of signature motifs. Thus, it is respectfully submitted that these references do not address the asserted utility of the claimed invention where the function is based upon signature motifs and/or Pfam domains. Furthermore, these three articles illustrate *exceptions*, and it is not possible to draw the conclusion that similar proteins will generally display different function. Indeed, it is stated in Seffernick *et al.* that:

> The present finding that proteins with >98% sequence identity catalyze different reactions in different metabolic pathways is *highly exceptional.*
> (see page 2409, column 1, lines 27-29 of Seffernick *et al.*; emphasis added)

In Witkowski *et al.*, a β-ketoacyl synthase was converted to a malonyl decarboxylase by directed mutagenesis of a cysteine nucleophile that belongs to the catalytic site (see page 11645, column 2, lines 11-15). On the contrary, as discussed above, the phosphatase signature motif and the residues involved in catalytic activity are conserved in SEQ ID NO: 399. Accordingly, the references cited by the Examiner would not lead one of skill in the art to question the assertion that a polypeptide displaying (1) a highly significant PAP2 Pfam domain; and (2) a phosphatase signature motif displaying the two absolutely conserved residues essential for enzyme function is a phosphatase.

Finally, Applicants respectfully submit that phosphatidic acid phosphatases have a substantial and well-established utility and that those skilled in the art would know how to use these enzymes. As illustrated by, *e.g.*, Abraham *et al.* and Brindley *et al.*, phosphatidic acid phosphatases play a role in decreasing cell division, obesity, insulin resistance, and cirrhosis (see *e.g.* Brindley *et al.*, page 51). Furthermore, the substrate of phosphatidic acid phosphatases is an intracellular second messenger in neutrophil activation and cytokine-dependent responses (see, *e.g.*, Abraham *et al.*, page 569, column 2, lines 15-16). Phosphatidic acid phosphatases are, thus, well-established therapeutic targets for treating diseases such as, *e.g.*, inflammatory diseases, obesity and insulin resistance. For example, SEQ ID NO: 399 can be used to identify agents which modulate its activity (see paragraph 1554 of US publication No. US-20030152921). It is respectfully submitted that this is a "real-word" use of SEQ ID NO: 399. Accordingly, reconsideration and withdrawal of the rejections set forth under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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Patent Attorney
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Gainesville, FL 32606-6669

FCE/dkt/sl
Attachments: formal Figure 1; Second Supplemental Information Disclosure Statement with references cited therein; HMM analysis is shown in Appendix 1

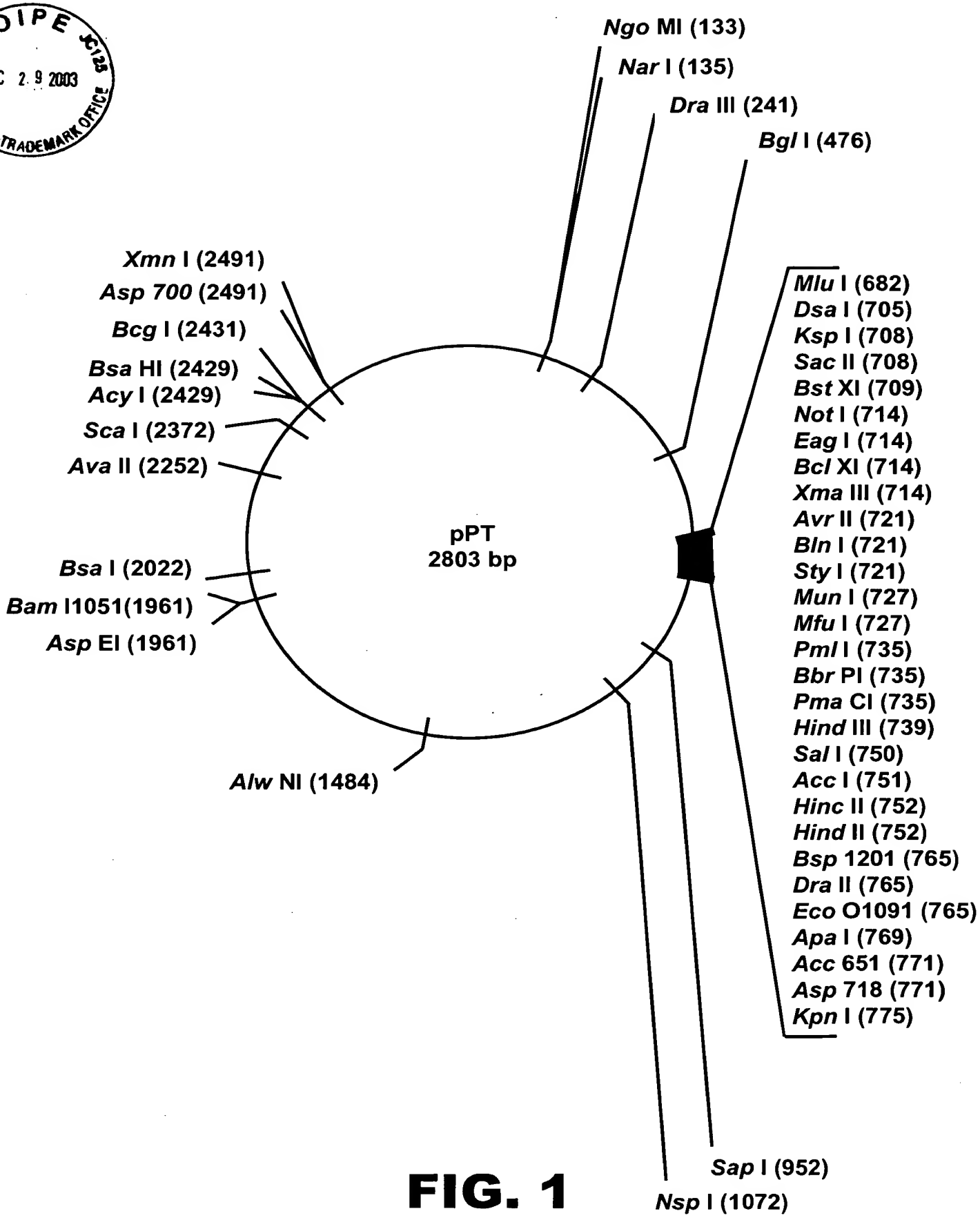

FIG. 1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 3

Complete if Known	
Application Number	09/876,997
Filing Date	June 8, 2001
First Named Inventor	Jean-Baptiste Dumas Milne Edwards
Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	G-078US04CIP

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Document Number Number - Kind Code [2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	U1	US-5,019,369	05/28/1991	Presant *et al.*	
	U2	US-5,872,141	02/16/1999	Umbreit *et al.*	
	U3	US-6,034,062	03/07/2000	Thies *et al.*	
	U4	US-6,204,060	03/20/2001	Mehtali *et al.*	
	U5	US-6,110,490	08/29/2000	Thierry	
	U6	US-6,242,179	06/05/2001	Shah *et al.*	
	U7	US-			
	U8	US-			
	U9	US-			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No. [1]	Foreign Patent Document Country Code [3] - Number [4] - Kind Code [5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T [6]
	F1					
	F2					
	F3					
	F4					
	F5					
	F6					
	F7					

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 3

Complete if Known	
Application Number	09/876,997
Filing Date	June 8, 2001
First Named Inventor	Jean-Baptiste Dumas Milne Edwards
Group Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	G-078US04CIP

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No. [1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T [2]
	R1	ABRAHAM, E., *et al.*, "Phosphatidic Acid Signaling Mediates Lung Cytokine Expression and Lung Inflammatory Injury After Hemorrhage in Mice", *J. Exp. Med.*, 1995, pages 569-575, Volume 181.	
	R2	BRINDLEY, D. and WAGGONER, D. "Phosphatidate phosphohydrolase and signal transduction", *Chem. Phys. Lipids*, 1996, pages 45-57, Volume 80.	
	R3	BURSTEN, S., *et al.*, "Potential Role for Phosphatidic Acid in Mediating the Inflammatory Responses to TNFα and IL-1β", *Circ. Shock*, 1994, pages 14-29, Volume 44.	
	R4	ENGLISH, D., "Phosphatidic Acid: A Lipid Messenger Involved in Intracellular and Extracellular Signalling", *Cell. Signal.*, 1996, pages 341-347, Volume 8, No. 5.	
	R5	ENGLISH, D., *et al.*, "Messenger functions of phosphatidic acid", *Chem. Phys. Lipids*, 1996, pages 117-132, Volume 80.	
	R6	KENT, C. "Eukaryotic Phospholipid Biosynthesis", *Ann. Rev. Biochem.*, 1995, pages 315-343, Volume 64.	
	R7	LEUNG, D., *et al.*, "CT-2576, an inhibitor of phospholipids signaling, suppresses constitutive and induced expression of human immunodeficiency virus", *Proc. Natl. Acad. Sci. USA*, 1995, pages 4813-4817, Volume 92.	
	R8	RICE, G., *et al.*, "Protection from endotoxic shock in mice by pharmacologic inhibition of phosphatidic acid", *Proc. Natl. Acad. Sci. USA*, 1994, 3857-3861, Volume 91.	
	R9	ROBERTS, R. and MORRIS, A. "Role of phosphatidic acid phosphatase 2a in uptake of extracellular lipid phosphate mediators", *Biochimica et Biophysica Acta*, 2000, pages 33-49, Volume 1487.	
	R10	SALVADOR, G.A., *et al.*, "Differential modulation of phospholipase D and phosphatidate phosphohydrolase during aging in rat cerebral cortex synaptosomes", *Exp. Gerontology*, 2002, pages 543-552, Volume 37.	
	R11	STUKEY, J. and CARMAN, G. "Identification of a novel phosphatase sequence motif", *Protein Science*, 1997, pages 469-472, Volume 6.	
	R12	Database GENBANK, Accession NP_003702; PANDEY, A.V., *et al.*, "Protein phosphatase 2A and phosphoprotein SET regulate androgen production by p450c17", *J. Biol. Chem.*, 2003, pages 2837-2844, Volume 278, Issue 5.	
	R13	Database GENBANK, Accession No. NP_795714; PANDEY, A.V., *et al.*, "Protein phosphatase 2A and phosphoprotein SET regulate androgen production by p450c17", *J. Biol. Chem.*, 2003, pages 2837-2844, Volume 278, Issue 5.	

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 3 of 3

Complete if Known	
Application Number	09/876,997
Filing Date	June 8, 2001
First Named Inventor	Jean-Baptiste Dumas Milne Edwards
Group Art Unit	1652
Examiner Name	Delia M. Ramirez
Attorney Docket Number	G-078US04CIP

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article, (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T[2]
	R14	Database GENBANK, Accession No. NP_803133; ISHIKAWA, T., *et al.*, "Cell surface activities of the human type 2b phosphatidic acid phosphatase", *J. Biochem.*, 2000, pages 645-651, Volume 127, Issue 4.	
	R15	Database GENBANK, Accession No. NP_808211; ZHANG, N., *et al.*, "Mice mutant for Ppap2c, a homolog of the germ cell migration regulator wunen, are viable and fertile", *Genesis*, 2000, pages 137-140, Volume 27, Issue 4.	
	R16	Accession No. AAB70690, Human hDPP protein sequence SEQ ID NO:7, May 17, 2001.	
	R17	JACOBS, K. *et al.* "A Novel Method for Isolating Eukaryotic cDNA Clones Encoding Secreted Proteins", *Dendritic Cells: Antigen Presenting Cells of T and B Lymphocytes*, March 10-16, 1995, page C1-207.	
	R18		
	R19		
	R20		
	R21		
	R22		
	R23		
	R24		
	R25		
	R26		

Examiner Signature		Date Considered	

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[1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

APPENDIX 1

HMMER 2.1.1 (Dec 1998)
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HMMER is freely distributed under the GNU General Public License (GPL).

Scores for sequence family classification (score includes all domains):

Model	Description	Score	E-value	N
PAP2	PAP2 superfamily	59.3	8.6e-14	1

Parsed for domains:

Model	Domain	seq-f	seq-t		hmm-f	hmm-t		score	E-value
PAP2	1/1	47	178	..	1	174	[]	59.3	8.6e-14

Alignments of top-scoring domains:

PAP2: domain 1 of 1, from 47 to 178: score 59.3, E = 8.6e-14

```
                 *->taigvlllalllaglllllknaigrlrplflalclpllalllncsd
                     a  +  lal+l+g++++ +k+ +gr+rp+f+ +c+p++++ ++
              47    QACLAASLALALNGVFTNTIKLIVGRPRPDFFYRCFPDGLAHSD--- 90

                 ggllkelfnrprPfthqfddsllstlelvheggySFPSGHssfaaaaaga
                   + + +       ++               v+eg++SFPSGHssfa+a++++
              91 -LMCTGDK-----DV-------------VNEGRKSFPSGHSSFAFAGLAF 121

                 lalllalrlrwrkSseSqlflsllrpllglllllallvglSRvylgvHy
                  +++la++l+ + +   q+++  +r ++ l +ll+a++++lSR  +++H+
             122 ASFYLAGKLHCFTP---QGRGKSWRFCAFLSPLLFAAVIALSRTCDYKHH 168

                 psDVlaGallGilvallvlllvrrlrd<-*
                 + D+l                  +  +
             169 WQDLL----------------KCTNT    178
```